REMARKS

Claims 1-113 were originally pending in this application. As the Examiner noted in a previous Office Action, claims 77-113 have been renumbered as claims 76-112. The Examiner's new numbering is set forth in the list of claims presented in this paper. Applicants previously canceled claims 84-100.

In the present Office Action, the Examiner withdrew claims 8, 29, 40, 46-82, and 101-112 as being directed to a non-elected invention. The Examiner also withdrew claims 19 and 33-37 as being directed to a non-elected species. With entry of this response, claims 38 and 39 are amended; and claims 83-100 are canceled, without prejudice or disclaimer. Thus, claims 1-82 are pending.

I. Restriction and Election of Species

The Examiner indicated that claims 83-100 have been canceled. Office Action, page 2. Applicants note, however, that prior to the renumbering of the claims, only claims 84-100 were canceled. See Amendment and Response to 2nd Restriction Requirement, filed April 11, 2003, page 1. Thus, an extra claim is included in the Examiner's summary of the canceled claims. In order to clarify the record, Applicants have now formally canceled claims 83-100.

Applicants thank the Examiner for clarifying the status of claim 19. Office Action, page 2. According to the Examiner, claim 19 is included in the elected invention (Group I), but is directed to a non-elected species. Thus, the Examiner withdrew the claim from further consideration.

Additionally, the Examiner withdrew claims 33-37, as being directed to a non-elected species. Office Action, page 2. Applicants note that the first page summary of

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the Office Action indicates claims 32-37 were withdrawn, but also indicates claims 30-39 were rejected (*i.e.*, still pending). After reviewing the status of these claims, Applicants believe that the statement in paragraph 3 of the Office Action is the correct one (*i.e.*, only claims 33-37 were withdrawn as being directed to a non-elected invention). Thus, claim 32 remains pending and has been rejected by the Examiner. Applicants respectfully request that the Examiner confirm the status of this claim.

In addition, Applicants respectfully remind the Examiner that if the elected species is found allowable, pursuant to M.P.E.P. § 803, the search should be expanded to include additional allowable species. In particular, if the Examiner finds that the elected species of introducing a nucleic acid into a target tissue by mechanical/physical means is patentable, Applicants believe that the withdrawn claims directed to introducing the nucleic acid via chemical/biochemical agents should be rejoined.

II. Claim to Priority

The Examiner acknowledged Applicants claim to priority based on French Application No. 001/10730, filed August 18, 2000. The Examiner indicated, however, that a certified copy of the priority document has not yet been received. Applicants are procuring the document and will submit it as soon as it is available.

III. The Claims Are Enabled

The Examiner rejected claims 1-7, 9-18, 20-28, 30-39 [sic], and 41-45, under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Office Action, pages 3-7. According to the Examiner, one of skill in the art would not be able to make and use the present invention without undue experimentation. *Id.*, page 3. In particular, the Examiner contends that a practitioner would not know how to (1) target a nucleic acid to

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specific animal cells, or (2) inhibit *in vivo* gene expression using an antisense nucleic acid that has been targeted to an animal cell. *Id.*, page 4. According to the Examiner, both of these steps "would have required experimentation to make and use the claimed invention because of the unpredictability of the art . . . and lack of guidance in the specification." *Id.* The Examiner notes that enablement issues are raised since the "USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. . . ." *Id.*, pages 3-4.

Applicants respectfully disagree. In traversing the rejection, Applicants note that the relevant inquiry for enablement is whether one of skill in the art could make or use the invention from the disclosure in the specification, coupled with information known in the art, without undue experimentation. *See* M.P.E.P. § 2164.01; *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Moreover, a patent need not teach, and preferably omits, what is well known in the art. *See* M.P.E.P. § 2164.01, and cases cited therein.

For the reasons discussed below, Applicants contend that one of skill in the art, using the teaching of the specification and the knowledge in the art, would know how to make and use the presently claimed invention without undue experimentation.

Contrary to the Examiner's position, the present specification provides a number of working examples that enable the presently claimed invention. First, Applicants have provided many examples in cell culture. *See* Specification, Example 7, pages 61-64. These cell culture experiments establish that the claimed invention functions to inhibit gene expression in a living cell. One of skill in the art, using this information, can then transfer the same genetic material into tissues in a living organism to achieve the same result.

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The specification provides confirmation of this fact with *in vivo* experiments. *See* Specification, Examples 8, 10, 11, and 13. These examples show the *in vivo* targeting of nucleic acids to specific tissues in mice (*e.g.*, skeletal muscle) using physical means (*e.g.*, electroporation/injection), and demonstrate the subsequent inhibition of gene expression in the transfected tissues. The experiments teach that the delivery of an individual nucleic acid molecule (sense or antisense alone) did not significantly alter the gene expression. But when the sense and antisense nucleic acids were co-transfected *in vivo*, gene expression was inhibited. Thus, the working examples show *in vivo* targeting of a transgene of interest and an inhibitory transgene to a specific tissue in an animal that results in the inhibition of gene expression.

Using these teachings, one of skill in the art can readily make and use the present invention. In addition, by modifying parameters that are either disclosed in the present specification or commonly known in the art, the skilled artisan can practice the claimed invention with other animals, transgenes and tissues. Such experimentation is routine. Thus, Applicants respectfully submit that these working *in vivo* examples teach one of skill in the art how to make and use the presently claimed invention without undue experimentation. In making the rejection, the Office has not presented any valid evidence to the contrary.

The Examiner cited several scientific publications to support his arguments concerning the "unpredictability" of the art. Applicants note that the Deonarain and Branch articles were published in 1998. Both review prior scientific literature. The bibliographic information indicates that these reviews are limited to scientific information published during 1997 and earlier. Applicants' invention, however, was filed in 2001

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and claims priority to an application filed in 2000. As the Examiner acknowledged, "progress has been made in recent years for *in vivo* gene transfer . . ." *Id.*, page 4. Thus, Applicants submit that these references do not accurately characterize the state of the art at the time the present invention was made.

The Examiner also cites Jen (2000) and Dias (2002), for their discussions of the challenges associated with using antisense as a therapy for disease. Applicants note that neither of the articles teach or suggest that antisense therapy doesn't work. In fact, the authors teach that the technology is routinely used in the art and cite dozens of publications that have reported successful applications of antisense oligonucleotide molecules. According to Dias, for example, ". . . oligonucleotides are commonly used in laboratories and clinical trials [to specifically and selectively downregulate gene expression] . . ." See Dias, Abstract, page 263.

Jen and Dias do express concerns about the efficiency and safety of using antisense molecules in the context of human gene therapies. The focus on efficiency of human therapies lends context to the statements quoted by the Examiner from these publications. For example, when Jen concludes that "it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive," the author is specifically referring to the absence of Phase III clinical studies using antisense molecules. See Jen, page 315, column 2, lines 9-12. Applicants are not required to provide a Phase III clinical trial to establish that the present invention is enabled. Moreover, Jen acknowledges that these antisense molecules have proven effective enough to warrant Phase I and Phase II clinical evaluations of the antisense gene therapy protocols. *Id.* Additionally, Applicants' own *in vivo* working examples

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demonstrate that any difficulties discussed by Jen and Dias that may be relevant to cells and tissues of human origin can, in fact, be overcome when practicing the presently claimed invention with cells and tissues of non-human origin.

While the Examiner may use these publications to argue about the "efficiency" of Applicants' claimed invention, this is not the standard for enablement. All that is required is for Applicants to teach one of skill in the art to practice the claimed invention without undue experimentation. Given the success reported in the art (*e.g.*, Phase I and II clinical trials and other publications cited in the review articles), combined with Applicants' own working *in vivo* examples, one of skill in the art is given sufficient guidance to make and use the presently claimed invention without undue experimentation.

In addition, Applicants note that the application, as filed, is *presumptively* enabled. In challenging the presumptively enabled patent application, the Examiner has cited the absence of working examples and made speculative statements about what might or might not be possible with gene transfer and inhibition of gene expression in human gene therapies. As noted above, there are many working examples (*in vitro* and *in vivo*) provided in the present specification. Moreover, the scientific publications do not teach that antisense therapies don't work or require undue experimentation. Rather, they describe the routine *in vivo* use of antisense molecules and highlight some of the challenges faced by those seeking to cure human disease using such molecules. Consequently, the Examiner's contentions are entirely insufficient to rebut the presumption of enablement.

Finally, Applicants respectfully remind the Examiner that the specification needs

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only to enable a single method of making and using the claimed invention. As long as the specification discloses at least one method for making and using the claimed invention, the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970); M.P.E.P. § 2164.01(b).

Applicants submit that the *in vivo* working examples discussed above (targeting antisense to mouse skeletal tissue) clearly demonstrates at least one method of making and using the claimed invention. The Examiner has argued that other uses might not be enabled (*e.g.*, delivering transgenes to other unspecified tissues). But when multiple uses are described, it is only necessary for Applicants to enable one of the uses. "[I]f any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." M.P.E.P. 2164.01(c). Thus, it is not necessary for Applicants to enable all of the other additional methods of making and using the claimed invention in order to satisfy the requirements of § 112, first paragraph.

For these reasons, Applicants contend that the present claims are enabled and respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 112, first paragraph.

IV. The Claims Are Not Indefinite

The Examiner rejected claims 38 and 39, under 35 U.S.C.§ 112, second paragraph, as allegedly being indefinite. According to the Examiner, these claims depend from an independent claim that is limited to nonhuman animal tissue or cells. Office Action, pages 7-8. Claims 38 and 39, however, recite nonhuman or human tissue. *Id.*, page 8. Applicants have amended claims 38 and 39 so they are consistent

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with the language recited in independent claim 1. Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: January 21, 2004

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